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Malignancy-related mortality following kidney transplantation is common

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There is a paucity of studies describing malignancy-related mortality after kidney transplantation. To help quantify this, we extracted data for all kidney-alone transplant procedures performed in England between April 2001 and March 2012. Data linkage analysis was performed between Hospital Episode Statistics and the Office for National Statistics to identify all deaths occurring in this cohort. Among 19,103 kidney transplant procedures analyzed (median follow-up 4.4 years), 2085 deaths occurred, of which 376 (18.0%) were due to malignancy (crude mortality rate 361 malignancy-related deaths per 100,000 person-years). Common sites of malignancy-related death were lymphoma (18.4%), followed by lung (17.6%) and renal (9.8%), with 14.1% unspecified. The risk of malignancy-related death increased with age: under 50 (0.8%), 50–59 (2.5%), 60–69 (4.8%), 70–79 (6.5%) and over 80 years (9.1%). Age- and gender-stratified malignancy-related mortality risk difference was higher in the transplant compared with the general population. Cox proportional hazard models identified increased age, pretransplant history of malignancy and deceased-donor kidney transplantation to be independently associated with risk for post-transplant death from malignancy. Thus, malignancy as a cause of post-kidney transplantation death is common and requires heightened surveillance.

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Kidney transplantation is widely attributed with an increased incidence of malignancy after transplantation versus the general population,^{1–3} and broadly on par with comparable immune deficiency states such as HIV/AIDS.⁴ The etiology of malignancy after transplant is primarily due to the effects of immunosuppression, with suggestions of an important interplay with viral pathogens that contributes to pathophysiology.⁵ By contrast, the literature on malignancy-related mortality after transplantation is scarce, with disparate mortality risk documented comparing solid organ transplant recipients to the general population.^{6,7} A similar analysis in a different cohort of patients such as in the United Kingdom has not been undertaken to confirm these findings. In addition, no study has yet provided information on the site of malignancy-related mortality in kidney transplantation and whether site-specific cancer mortality can be stratified along demographic factors such as age, gender and/or ethnicity.

To inform clinical practice, we undertook a population-based cohort analysis of all deaths occurring after kidney transplantation in England over the past decade to determine causes, classifications and predictors of malignancy-related mortality. The aim of our study was to determine the overall and site-specific risk for malignancy-related mortality after kidney transplantation.

RESULTS

A total of 19,688 kidney transplant procedures in England were recorded in the Hospital Episode Statistics (HES) data for adult (18,499) and pediatric ($n = 1189$) kidney allograft recipients—excluding those with missing demographic data ($n = 585$), we had a cohort of 19,103 for further analysis (104,154 patient-years for entire study cohort). There was no missing data with regard to mortality events.

Table 1 demonstrates baseline characteristics of our study cohort. The median age for the whole cohort was 45 years (interquartile range 34–55 years). In all, 11,673 (61.1%) of the study cohort were men, with 7430 (38.9%) women. Ethnic breakdown of the study cohort comprised of white (13,695, 71.7%), Black or Black British (934, 4.9%), Asian or Asian British (1704, 8.9%), Chinese (81, 0.4%), mixed (166, 0.9%),

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Table 1 | Baseline characteristics of kidney allograft recipients

Variable	Proportion (%)
Age (years)	
<50	9060 (47.6%)
50–59	4562 (23.9%)
60–69	3733 (19.5%)
70–79	1631 (8.5%)
≥80	117 (0.6%)
Gender	
Male	11,673 (61.1%)
Female	7430 (38.9%)
Ethnicity	
White	13,695 (71.7%)
Black/Black British	934 (4.9%)
Asian/Asian British	1704 (8.9%)
Chinese	81 (0.4%)
Mixed	166 (0.9%)
Other	350 (1.8%)
Unknown	2173 (11.4%)
Socioeconomic deprivation (IMD 2010)	
1 (most deprived)	4203 (22.0%)
2	4197 (22.0%)
3	3765 (19.7%)
4	3490 (18.3%)
5 (least deprived)	3448 (18.0%)
Donor	
Living	6262 (32.8%)
Deceased	12,841 (67.2%)

Abbreviation: IMD, index of multiple deprivation.

other ethnic group (350, 1.8%), and unknown (2173, 11.4%). Socioeconomic deprivation quintiles were (from most to least deprived, respectively): 1 (4203, 22.0%), 2 (4,197, 22.0%), 3 (3765, 19.7%), 4 (3490, 18.3%), and 5 (3448, 18.0%). Living donor transplantation occurred in 6262 (32.8%) of all kidney transplant procedures reported. Diabetes mellitus classification was the most common medical comorbidity recorded in 2968 (15.5%) of all kidney allograft recipients.

Data accuracy

To verify the quality of the HES data, we extracted information from the UK National Transplant database to determine the number of transplants performed during the same time frame. During the time from April 2001 and March 2012, 19,405 kidney transplant procedures were registered (19,241 kidney alone, 49 *en bloc* kidneys and 115 double kidneys transplants). This identifies a small discrepancy of 283 kidney-alone transplant procedures that have been over-reported in the HES data in comparison to UK National Transplant Database records (concordance 98.6% between both data sets). However, it should be highlighted that HES data records ‘date of admission’, whereas UK National Transplant database registers ‘date of transplant’, which could contribute to this apparent incongruity.

Cancer mortality after kidney transplantation

By cross-referencing both HES and Office for National Statistics (ONS) databases, we identified 2085 deaths that occurred after kidney transplantation with median follow-up 4.4 years (interquartile range 2.2–7.3 years). Follow-up time consisted of 104,154 patient-years, with similar 4.4 years median follow-up in patient-years. Three hundred and seventy-six deaths were due to malignancy (2.0% of overall study cohort and 18.0% of total deaths). This equates to a crude mortality rate of 361 malignancy-related deaths per 100,000 person-years in our study cohort. Only death from infection (20.8%, 416 deaths per 100,000 person-years) and cardiovascular disease (21.2%, 424 deaths per 100,000 person-years) was more frequently documented as the leading cause of death. The most common site of malignancy-related death was lymphoma (18.4% of all cancer-related deaths), followed by lung (17.6%) and renal (9.8%), respectively (14.1% were unspecified).

Age-, sex-, and ethnicity-specific malignancy mortality rate

Table 2 highlights the risk for malignancy-related death (all-cause and location-specific) for our study cohort stratified by age, gender, and ethnicity. Age was an important and strong risk factor for cancer-related death, with increasing risk for cancer-related death as age increased: <50 (0.8%), 50–59 (2.5%), 60–69 (4.8%), 70–79 (6.5%), and over 80 (9.1%). There were only five malignancy-related deaths in the pediatric cohort (aged under 18 years) and all were classified as caused by lymphoma. Table 2 demonstrates the split in location of malignancy-related deaths into three age brackets of <50, 50–69, and over 70 years, respectively.

Lung cancer was the most common malignancy-related death in men (18.6% of all cancer deaths), with lymphoma cancer being the most common in women (18.7% of all cancer deaths). There was no significant difference in the rate of cancer-related death or location of cancer with ethnicity in our cohort, although a trend was observed toward less overall malignancy-related death in non-whites (1.3%) versus whites (2.1%) ($P=0.077$), respectively. In a comparative analysis of transplant versus general population, Figure 1 compares the age-stratified mortality risk difference between the transplant and general population and demonstrates higher malignancy-related mortality risk in the transplant cohort for the majority of age groups. Figure 2 compares gender-stratified mortality risk difference between the transplant and general cohort and again demonstrates higher malignancy-related mortality risk for both male and female kidney allograft recipients versus the general population. No comparative analysis for ethnicity was performed because of the absence of robust mortality data for England based on ethnicity.

In addition to the above demographic stratifications, we compared live-donor versus deceased-donor kidney transplant recipients for risk of malignancy-related death. We found live-donor kidney allograft recipients had a lower risk of malignancy-related death versus deceased-donor kidney allograft recipients (1.1% vs. 2.4%, respectively; $P<0.001$).

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